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(71) Applicant *(for all designated States except US)*: MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LEGER, Serge [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GRIMM, Erich [DE/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). PRASIT, Petpiboon [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(74) Agent: MURPHY, Kevin, P.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College, Montreal, Quebec H3A 2Y3 (CA).

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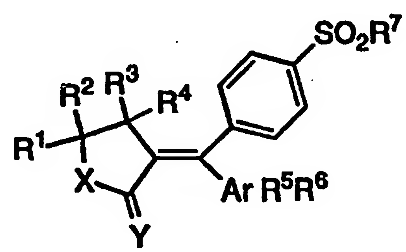
(54) Title: ALPHA-METHYLENE GAMMA LACTONES AS SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract

The invention encompasses the novel compound of Formula (I) as well as a method of treating COX-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula (I). The invention also encompasses certain pharmaceutical compositions for treatment of COX-2 mediated diseases comprising compounds of Formula (I).



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TITLE OF THE INVENTION

ALPHA-METHYLENE GAMMA LACTONES AS SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the COX-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, COX-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, COX-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of COX-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced

potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Furthermore, such a compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for the treatment of glaucoma.

The potential utilities of selective cyclooxygenase-2 inhibitors are discussed in the following articles:

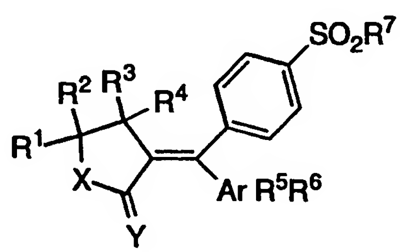
1. John Vane, "Towards a better aspirin" in Nature, Vol. 367, pp. 215-216, 1994

2. Bruno Battistini, Regina Botting and Y.S. Bakhle, " COX-1 and COX-2: Toward the Development of More Selective NSAIDs" in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

3. David B. Reitz and Karen Seibert, "Selective Cyclooxygenase Inhibitors" in Annual Reports in Medicinal Chemistry , James A. Bristol, Editor, Vol. 30, pp. 179-188, 1995.

SUMMARY OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating COX-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.

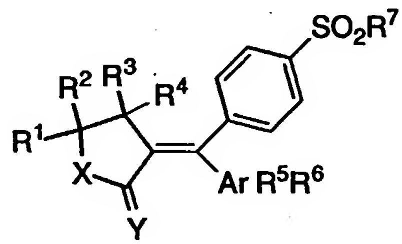


I

The invention also encompasses certain pharmaceutical compositions for treatment of COX-2 mediated diseases comprising compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating COX-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



I

X is
(a) O,
(b) CH_2,
(c) $CH(C_{1-3}alkyl)$,
(d) $C(C_{1-3}alkyl)_2$ or
(e) a bond;

Y is
(a) O,
(b) H,OH or
(c) H,H;

Ar is
(a) phenyl or
(b) pyridyl;

each of R^1, R^2, R^3, or R^4 is independently
(a) hydrogen or,
(b) $C_{1-6}alkyl$;

each of R^5 or R^6 is independently
(a) hydrogen,

(b) halo,
(c) C_{1-4}alkyl,
(d) C_{1-4}alkoxy, or
(e) C_{1-4}alkylthio;

R^7 is (a) NH_2 or
(b) CH_3.

A preferred embodiment of the invention is that wherein X is O.

Another preferred embodiment of the invention is that wherein Y is O.

Another preferred embodiment of the invention is that wherein X and Y are both O.

Another preferred embodiment of the invention is that wherein R^1 and R^2 are both CH_3.

Another preferred embodiment of the invention is that wherein R^5 is hydrogen or F.

Another preferred embodiment of the invention is that wherein R^7 is CH_3.

Exemplifying this invention are:

3-[(E)-1-(4-(Methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone,

5,5-Dimethyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone,

3-[(E)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl]-methylidene]tetrahydro-2-furanone,

3-[(Z)-1-(3-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylidene]tetrahydro-2-furanone,

5-Methyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenyl-methylidene]tetrahydro-2-furanone,

3-[(E)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-methylidene]-5,5-dimethyltetrahydro-2-furanone,

3-[(Z)-1-(3-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-methylidene]-5,5-dimethyltetrahydro-2-furanone,

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(2-pyridyl)methylidene] tetrahydro-2-furanone,

3-[(Z)-1-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylidene]-5,5-dimethyltetrahydro-2-furanone,

4,4-Dimethyl-3-[1-(4-(methylsulfonyl)phenyl)-1-phenyl-methylidene]tetrahydro-2-furanone,

4-[Cyclopentyliden(phenyl)methyl]phenyl methyl sulfone,

2[(E)-1-(4-(Methylsulfonyl)phenyl)-1-phenylmethylidene]-1-cyclopentanone, 5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(3-pyridyl)methylidene] tetrahydro-2-furanone,

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(4-pyridylmethylidene] tetrahydro-2-furanone, and

4-[Cyclobutyliden(phenyl)methyl]phenyl methyl sulfone.

The following abbreviations have the indicated meanings:

AA	=	arachidonic acid
Ac	=	acetyl
AIBN	=	2.2¯-azobisisobutyronitrile
Bn	=	benzyl
CSA	=	camphor sulfonic acid
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et_3N	=	triethylamine
HBSS	=	Hanks balanced salt solution
HEPES	=	N-[2-Hydroxyethyl]piperazine-N^1-[2-ethanesulfonic acid]
HWB	=	human whole blood
KHMDS	=	potassium hexamethyldisilazane
LDA	=	lithium diisopropylamide
LPS	=	lipopolysaccharide
MMPP	=	magnesium monoperoxyphthalate
Ms	=	methanesulfonyl = mesyl
Ms0	=	methanesulfonate = mesylate
NSAID	=	non-steroidal anti-inflammatory drug
OXONE™	=	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate

Ph	=	phenyl
r.t.	=	room temperature
rac.	=	racemic
Tf	=	trifluoromethanesulfonyl = triflyl
Tf0	=	trifluoromethanesulfonate = triflate
TFOH	=	trifluoromethane sulfonic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
Ts	=	p-toluenesulfonyl = tosyl
TsO	=	p-toluenesulfonate = tosylate
SO_2Me	=	methyl sulfone
SO_2NH_2	=	sulfonamide

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

Dose Abbreviations

bid	=	bis in die = twice daily
qid	=	quater in die = four times a day
tid	=	ter in die = three times a day

The term "alkyl" means linear, branched or cyclic structures and combinations thereof, containing the indicated number of carbon atoms. Examples of alkyl groups include methyl, ethyl, cyclopropyl, isopropyl, butyl, t-butyl, pentyl, hexyl, cyclohexyl, heptyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl- 4-propylnonyl, and the like.

"Alkoxy" means alkoxy groups of the indicated number of carbon atoms of a straight, branched, or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

"Alkylthio" means alkylthio groups of the indicated number of carbon atoms of a straight, branched or cyclic configuration. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

Halogen includes F, Cl, Br, and I.

In another embodiment , the invention encompasses pharmaceutical compositions for inhibiting COX-2 and for treating COX-2 mediated diseasesas disclosed herein comprising a pharmaceutically acceptable carrier and non-toxic therapeutically effective amount of a compound of formula I as described above.

In yet another embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centres and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, adipic, aspartic, 1,5-naphthalenedisulfonic, benzenesulfonic, benzoic, camphorsulfonic, citric, 1,2-ethanedisulfonic, ethanesulfonic, ethylenediaminetetraacetic, fumaric, glucoheptonic, gluconic, glutamic, hydriodic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, 2-naphthalenesulfonic, nitric, oxalic, pamoic, pantothenic, phosphoric, pivalic, propionic, salicylic, stearic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, undecanoic, 10-undecenoic, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, methanesulfonic, phosphoric, sulfuric and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumour growth and hence can be used in the treatment of cancer. Compound 1 may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for treatment of glaucoma.

By virtue of its high inhibitory activity against COX-2 and/or its specificity for COX-2 over COX-1, compound I will prove useful as an alternative to conventional NSAID'S, particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anaemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Pharmaceutical Compositions

For the treatment of any of these cyclooxygenase mediated diseases compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical

compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as

polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxy-ethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous

suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Dose Ranges

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary

depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Combinations with Other Drugs

Similarly, compound I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating COX-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H_2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol: a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of

Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

Methods of Synthesis

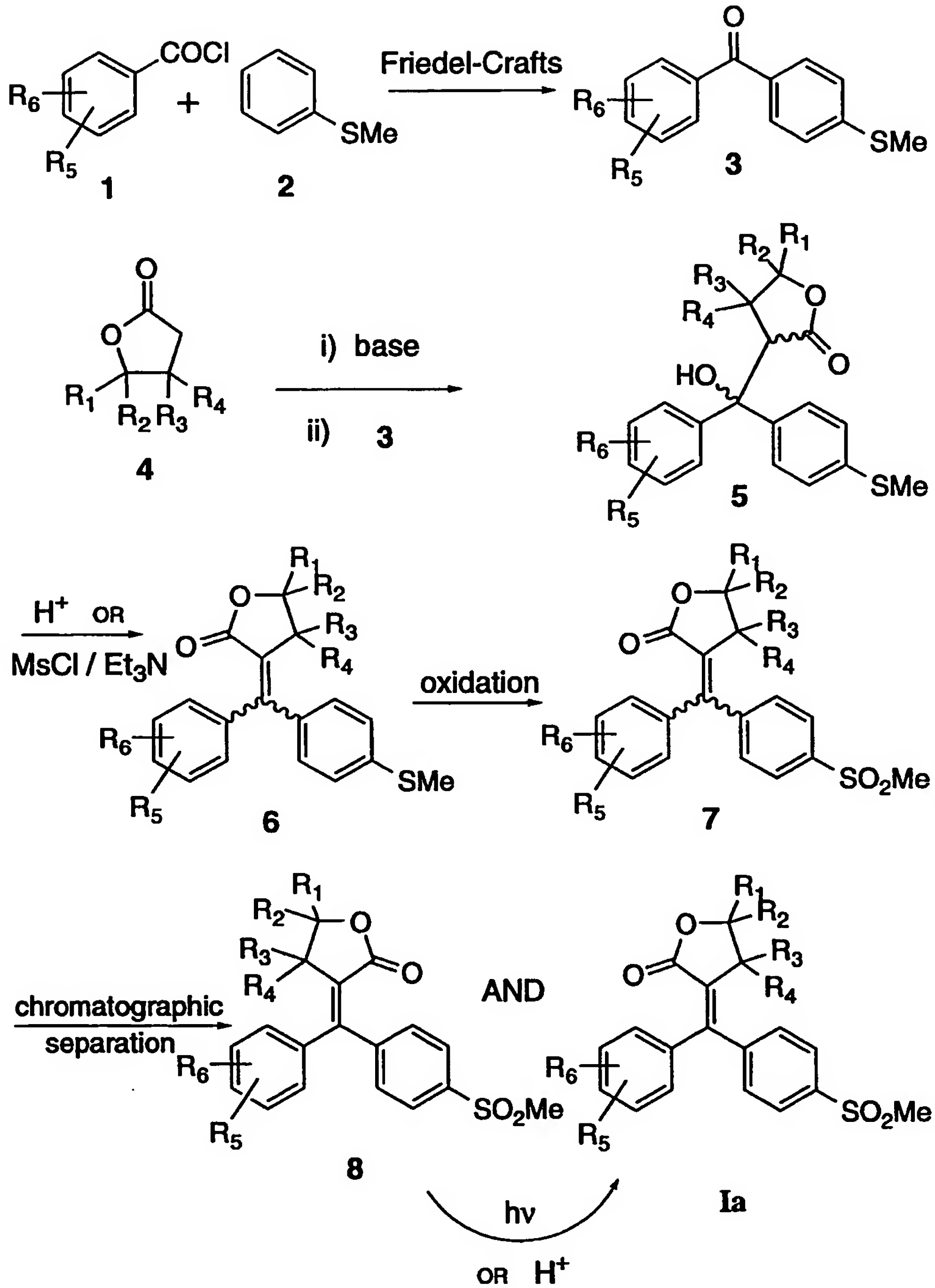
The compounds of the present invention can be prepared according to the following methods.

Method 1

A Friedel-Crafts reaction between a benzoyl chloride 1 and thioanisole 2 yields benzophenone 3. Lactone 4 is condensed with 3 using a suitable base such as LDA to give alcohol 5. Alcohol 5 is dehydrated to 6 using an acid, such as TfOH or CSA or by conversion to the mesylate; 6 is obtained as a mixture of the E and Z isomers. Sulfide 6 is oxidized to the sulfone mixture 7 using MMPP or OXONE™ , followed by chromatographic separation to obtain compound Ia.

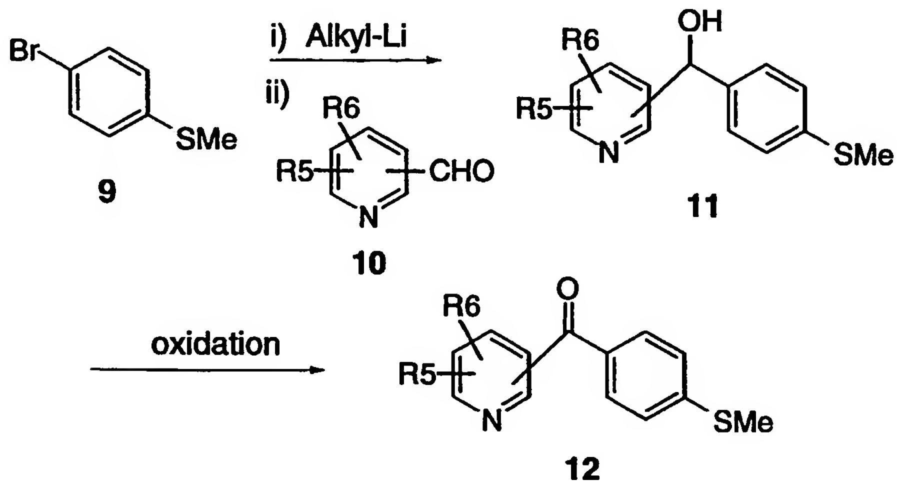
Alternatively, the mixture of isomers 6 can be separated and the desired precursor to Ia oxidized. The undesired isomer of 6, and compound 8, can be isomerized to the desired isomers by treatment with a protonic acid or by photochemical means.

To prepare the compounds I in which Ar is pyridyl, the ketone 12 (Method 2) is used in place of benzophenone 4. In this case, the oxidation step (6 - 7) is done with OXONE™ in order to avoid formation of a pyridine-N-oxide.


COCl
SMe
Friedel-Crafts
1
2
3
i) base
ii) 3
4
5
H+ OR
MsCl / Et3N
oxidation
SO2Me
6
7
chromatographic separation
AND
8
Ia
hν
OR H+

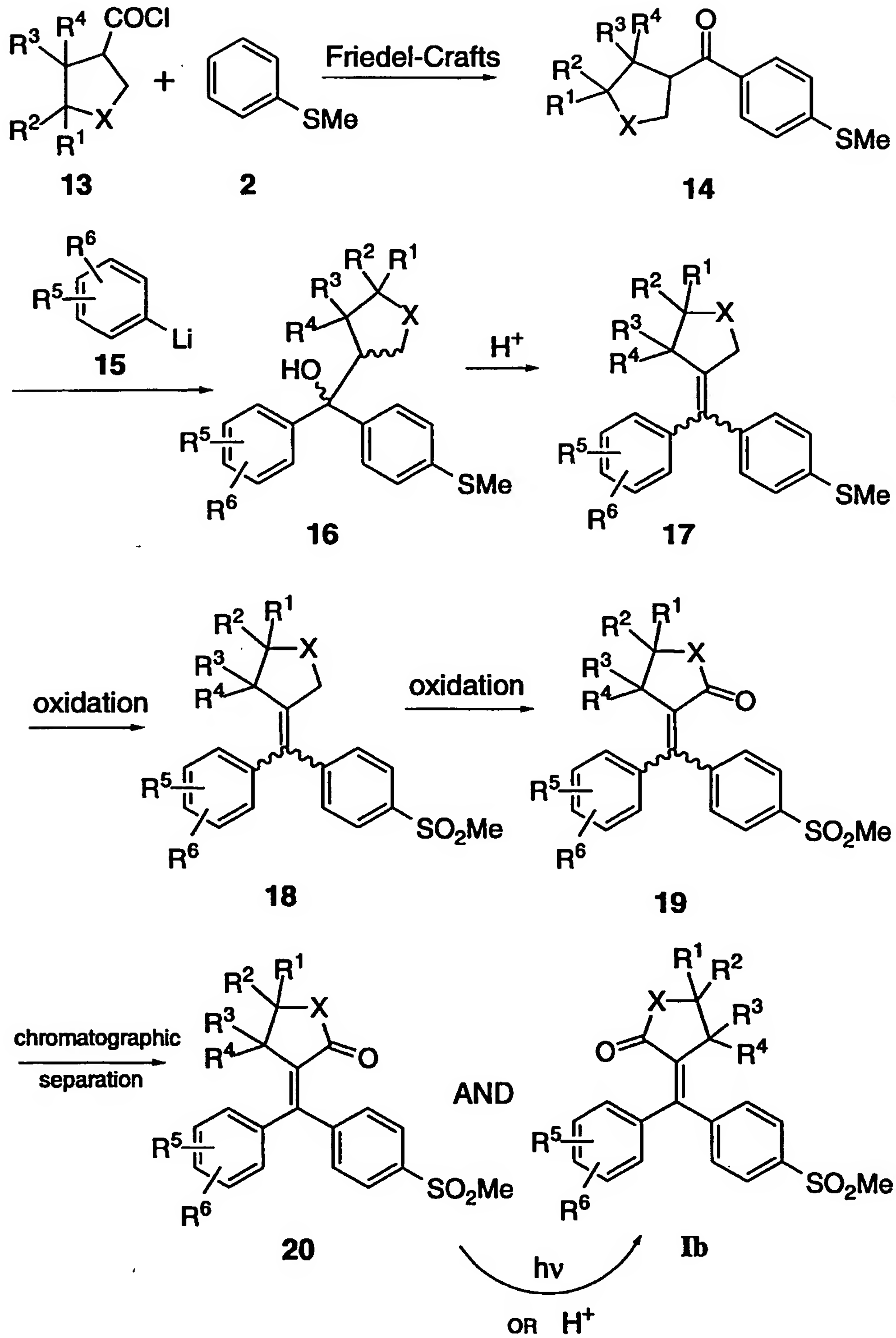
Method 2

Bromothioanisole 9 is transmetallated with an alkyl lithium, followed by reaction with aldehyde 10, to produce alcohol 11. Oxidation with a mild reagent such as MnO_2 in ethyl acetate gives ketone 12, which is then used in place of benzophenone 3 in Method 1.



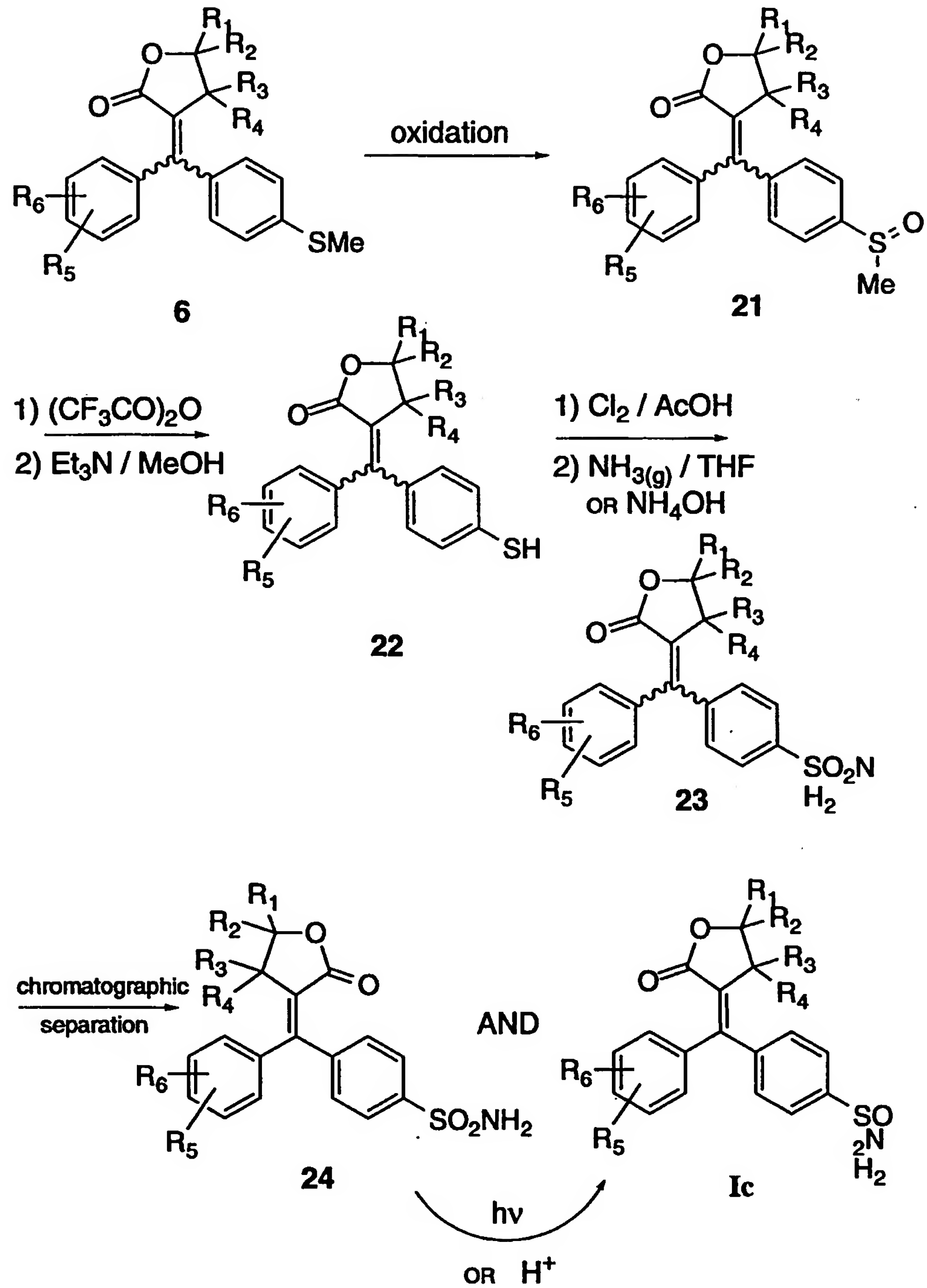
Method 3

A Friedel-Crafts reaction between acid chloride 13 and thioanisole 2 yields the ketone 14, which upon reaction with an aryl lithium 15 yields tertiary alcohol 16. Dehydration of the latter with a proton acid produces a mixture of the stereoisomers 17, which is oxidized to the mixture of sulfones 18 by MMPP or other suitable oxidant. Allylic oxidation with a reagent such as chromium trioxide yields 19 as a mixture of isomers. Chromatographic separation then yields the stereoisomers 20 and Ib.


COCl
Friedel-Crafts
SMe
13
2
14
15
Li
HO
H+
16
17
oxidation
SO2Me
18
19
chromatographic
separation
AND
20
Ib
hν
OR H+

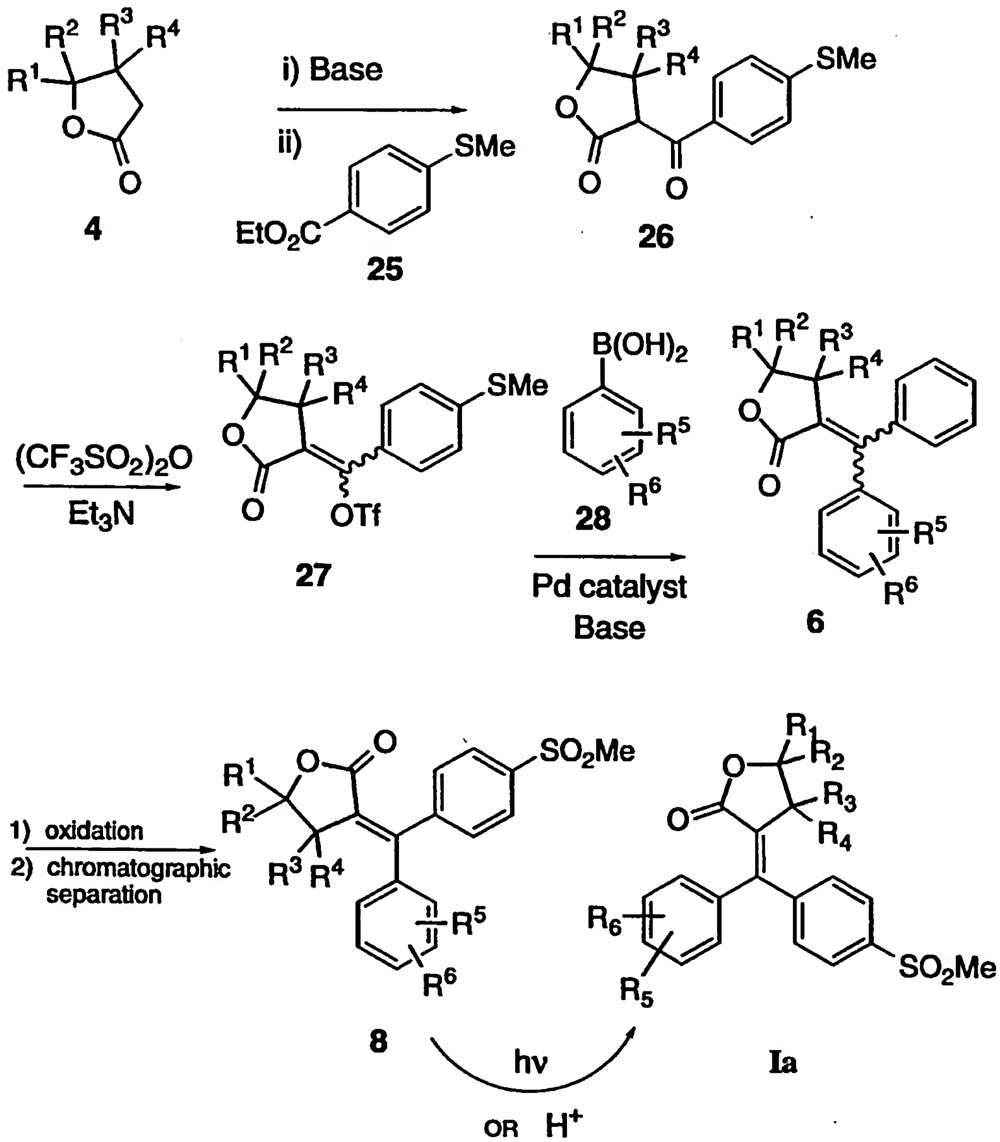
Method 4

Preparation of the sulfonamides ($R^7 = NH_2$) is carried out according to Method 4. The intermediate 6 can be selectively oxidized to sulfoxide 21 by using one equivalent of an oxidizing agent such as MMPP. The free thiol 22 is obtained by reacting 21 with trifluoroacetic anhydride, followed by treatment with triethylamine in methanol. Oxidation of thiol 22 with Cl_2 in acetic acid yields a sulfonyl chloride intermediate, which reacts with ammonia to yield the isomeric mixture of sulfonamide 23. The isomers are separated by chromatography to yield 24 and the desired Ic.


oxidation
6
21
1) $(CF_3CO)_2O$
2) Et_3N / MeOH
22
1) Cl_2 / AcOH
2) $NH_{3(g)}$ / THF OR NH_4OH
23
chromatographic separation
24
AND
Ic
hν OR H^+

Method 5

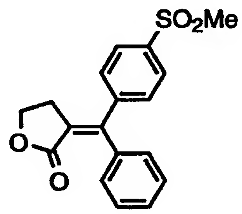
An alternative preparation of Ia is outlined in Method 5. Condensation of lactone 4 with ester 25 is brought about by reaction with an anhydrous base such as LDA to yield ketolactone 26. The enol triflate 27 is obtained as a mixture of stereoisomers by reacting 25 with triflic anhydride. A Suzuki coupling of 27 and 28 yields the mixture of stereoisomers 6, which is carried through to compound Ia as in Method 1.



Representative Compounds

Table I illustrates compounds of formula I, which are representative of the present invention.

Example 1



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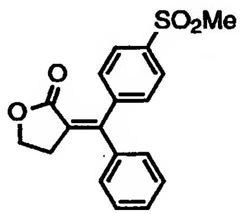
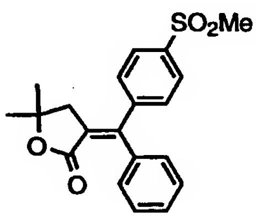
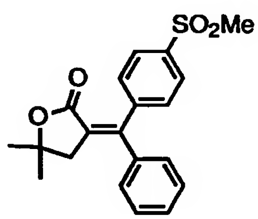


Example 3



Example 4



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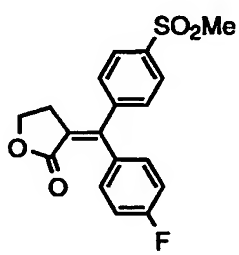

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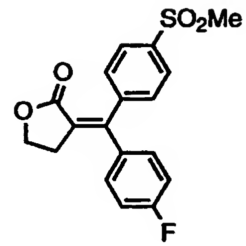

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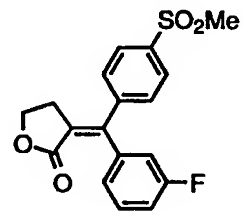

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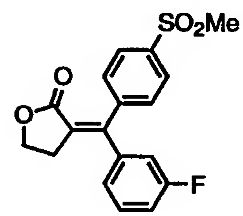

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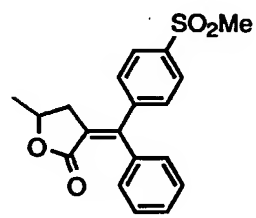

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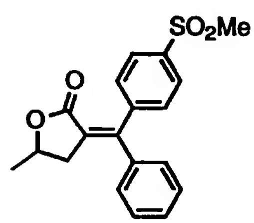

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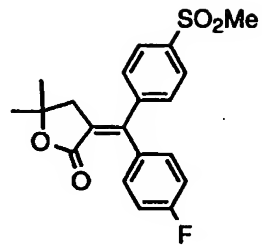

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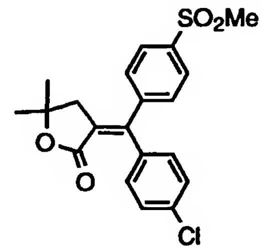

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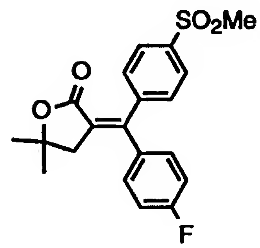

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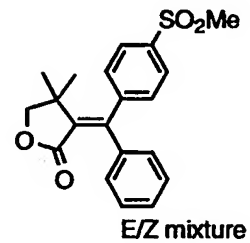

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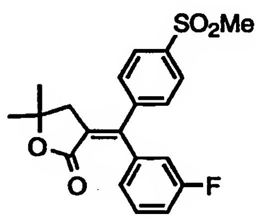

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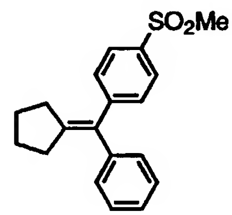

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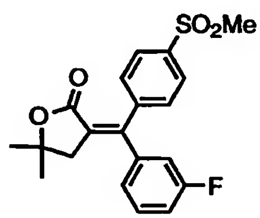

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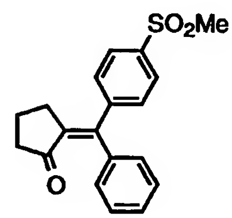

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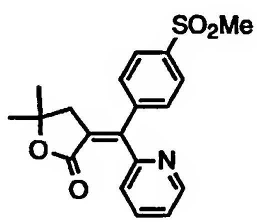

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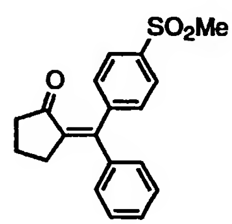
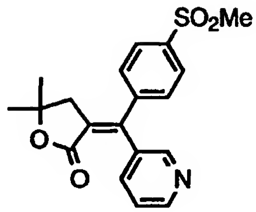
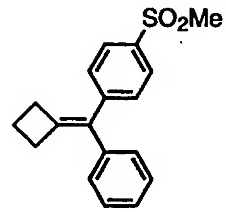


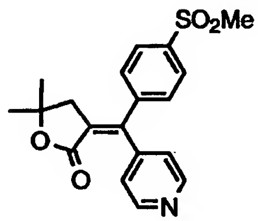
Example 21



Example 23



Example 22



Assays for Determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their COX-2 inhibiting activity.

INHIBITION OF CYCLOOXYGENASE ACTIVITY

Whole cell assays for COX-2 and COX-1 using CHO transfected cell lines

Chinese hamster ovary (CHO) cell lines which have been stably transfected with an eukaryotic expression vector pCDNAIII containing either the human COX-1 or COX-2 cDNA's are used for the assay. These cell lines are referred to as CHO [hCOX-1] and CHO [hCOX-2], respectively. For cyclooxygenase assays, CHO[hCOX-1] cells from suspension cultures and CHO[hCOX-2] cells prepared by trypsinization of adherent cultures are harvested by centrifugation (300 x g, 10 min) and washed once in HBSS containing 15 mM HEPES, pH 7.4, and resuspended in HBSS, 15 mM HEPES, pH 7.4, at a cell concentration of 1.5 x 10^6 cells/ml. Drugs to be tested are dissolved in DMSO to 66.7-fold the highest test drug concentration. Compounds are typically tested at 8 concentrations in duplicate using serial 3-fold serial dilutions in DMSO of the highest drug concentration. Cells (0.3 x 10^6 cells in 200 µl) are preincubated with 3 µl of the test drug or DMSO vehicle for 15 min at 37C. Working solutions of peroxide-free AA (5.5 µM and 110 µM AA for the CHO [hCOX-1] and CHO [COX-2] assays, respectively) are prepared by a 10-fold dilution of a concentrated AA solution in ethanol into HBSS

containing 15 mM HEPES, pH 7.4. Cells are then challenged in the presence or absence of drug with the AA/HBSS solution to yield a final concentration of 0.5 μM AA in the CHO[hCOX-1] assay and a final concentration of 10 μM AA in the CHO[hCOX-2] assay. The reaction is terminated by the addition of 10 μl 1 N HCl followed by neutralization with 20 μl of 0.5 N NaOH. The samples are centrifuged at 300 x g at 4C for 10 min, and an aliquot of the clarified supernatant is appropriately diluted for the determination of PGE_2 levels using an enzyme-linked immunoassay for PGE_2 (Correlate PGE_2 enzyme immunoassay kit, Assay Designs, Inc.). Cyclooxygenase activity in the absence of test compounds is determined as the difference in PGE_2 levels of cells challenged with arachidonic acid versus the PGE_2 levels in cells mock-challenged with ethanol vehicle. Inhibition of PGE_2 synthesis by test compounds is calculated as a percentage of the activity in the presence of drug versus the activity in the positive control samples.

Assay of COX-1 Activity from U937 cell microsomes

U 937 cells are pelleted by centrifugation at 500 x g for 5 min and washed once with phosphate-buffered saline and repelleted. Cells are resuspended in homogenization buffer consisting of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2 μg/ml leupeptin, 2 μg/ml soybean trypsin inhibitor, 2 μg/ml aprotinin and 1 mM phenyl methyl sulfonyl fluoride. The cell suspension is sonicated 4 times for 10 sec and is centrifuged at 10,000 x g for 10 min at 4° C. The supernatant is centrifuged at 100,000 x g for 1 hr at 4° C. The 100,000 x g microsomal pellet is resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA to approximately 7 mg protein/ml and stored at -80° C.

Microsomal preparations are thawed immediately prior to use, subjected to a brief sonication, and then diluted to a protein concentration of 125 μg/ml in 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA, 0.5 mM phenol, 1 mM reduced glutathione and 1 μM hematin. Assays are performed in duplicate in a final volume of 250 μl. Initially, 5 μl of DMSO vehicle or drug in DMSO are added to 20 μl of 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA in wells of a 96-deepwell polypropylene titre plate. 200 μl of the microsomal preparation are then added and pre-incubated for 15 min at room temperature before

addition of 25 µl of 1 M arachidonic acid in 0.1 M Tris-HCl and 10 mM EDTA, pH 7.4. Samples are incubated for 40 min at room temperature and the reaction is stopped by the addition of 25 µl of 1 N HCl. Samples are neutralized with 25 µl of 1 N NaOH prior to quantitation of PGE_2 content by radioimmunoassay (Dupont-NEN or Amersham assay kits). Cyclooxygenase activity is defined as the difference between PGE_2 levels in samples incubated in the presence of arachidonic acid and ethanol vehicle.

Assay of the activity of purified human COX-2

The enzyme activity is measured using a chromogenic assay based on the oxidation of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) during the reduction of PGG_2 to PGH_2 by COX-2 (Copeland et al. (1994) Proc. Natl. Acad. Sci. 91, 11202-11206).

Recombinant human COX-2 is purified from Sf9 cells as previously described (Percival et al (1994) Arch. Biochem. Biophys. 15, 111-118). The assay mixture (180 µL) contains 100 mM sodium phosphate, pH 6.5, 2 mM genapol X-100, 1 µM hematin, 1 mg/ml gelatin , 80-100 units of purified enzyme (One unit of enzyme is defined as the amount of enzyme required to produce an O.D. change of 0.001/min at 610 nm) and 4 µL of the test compound in DMSO. The mixture is pre-incubated at room temperature (22°C) for 15 minutes prior to initiation of the enzymatic reaction by the addition of 20 µL of a sonicated solution of 1 mM arachidonic acid (AA) and 1 mM TMPD in assay buffer (without enzyme or hematin). The enzymatic activity is measured by estimation of the initial velocity of TMPD oxidation over the first 36 sec of the reaction. A non-specific rate of oxidation is observed in the absence of enzyme (0.007 - 0.010 O.D. /min) and is subtracted before the calculation of the % inhibition. IC_{50} values are derived from 4-parameter least squares non-linear regression analysis of the log-dose vs % inhibition plot.

HUMAN WHOLE BLOOD ASSAY

Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE_2 production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS, which induces COX-2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE_2 production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B_2 (TxB_2) via activation of COX-1. Thus, the effect of test compounds on TxB_2 levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE_2 after LPS induction (COX-2) and TxB_2 following blood clotting (COX-1) in the same assay.

<u>Method</u>

<u>A. COX-2 (LPS-induced PGE_2 production)</u>

Fresh blood is collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects have no apparent inflammatory conditions and have not taken any NSAIDs for at least 7 days prior to blood collection. Plasma is immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE_2). The remaining blood is incubated with LPS (100 μg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA (Phosphate buffered saline) for 5 minutes at room temperature. Five hundred μL aliquots of blood are incubated with either 2μL of vehicle (DMSO) or 2μL of a test compound at final concentrations varying from 10nM to 30μM for 24 hours at 37°C. At the end of the incubation, the blood is centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100μL aliquot of plasma is mixed with 400μL of methanol for protein precipitation. The supernatant is obtained and is assayed for PGE_2 using a radioimmunoassay kit (Amersham, RPA#530) after conversion

of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

B. COX-1 (Clotting-induced TxB_2 production)

Fresh blood is collected into vacutainers containing no anticoagulants. Aliquots of 500μL are immediately transferred to siliconized microcentrifuge tubes preloaded with 2μL of either DMSO or a test compound at final concentrations varying from 10nM to 30μM. The tubes are vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum is obtained by centrifugation (12,000 x g for 5 min.). A 100μL aliquot of serum is mixed with 400μL of methanol for protein precipitation. The supernatant is obtained and is assayed for TxB_2 using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

RAT PAW EDEMA ASSAY

Protocol

Male Sprague-Dawley rats (150-200 g) are fasted overnight and are given, po, either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line is drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_0) is measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarly with 50 μl of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 μg carrageenan per paw). Three hr later, the paw volume (V_3) is measured and the increases in paw volume ($V_3 - V_0$) are calculated. The animals are sacrificed by CO_2 asphyxiation and the absence or presence of stomach lesions scored. Data is compared with the vehicle-control values and percent inhibition calculated. All treatment groups are coded to eliminate observer bias.

NSAID-INDUCED GASTROPATHY IN RATS

Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of Cox-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal ^{51}Cr excretion after systemic injection of ^{51}Cr-labeled red blood cells. Fecal ^{51}Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of ^{51}Cr-labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water ad *lib*. Feces are collected for a 48 h period and ^{51}Cr fecal excretion is calculated as a percent of total injected dose. ^{51}Cr-labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 µCi of sodium ^{51}chromate for 30 min. at 37°C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium ^{51}chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 µCi) is injected per rat.

PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard non-steroidal anti-inflammatory drugs (NSAIDs). This can be quantitatively assessed by

intravenous administration of $^{51}CrCl_3$ solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocell or 5% Tween 80 in H_2O vehicles, (3mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous ^{51}Cr (5 μCi/kg in 1 ml/kg phosphate buffer saline (PBS)) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted ^{51}Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

LPS-Induced Pyrexia in Conscious Rats

Male Sprague-Dawley rats (150 - 200 g) were fasted for 16 - 18 h before use. At approximately 9:30 a.m., the animals were placed temporarily in plexiglass restrainers and their baseline rectal temperature was recorded using a flexible temperature probe (YSI series 400) connected to a digital thermometer (Model 08502, Cole Parmer). The same probe and thermometer were used for all animals to reduce experimental error. The animals were returned to their cages after the temperature measurements. At time zero, the rats were injected intraperitoneally with either saline or LPS (2 mg/kg, Sigma Chem) and the rectal temperature was remeasured at 5, 6 and 7 h following LPS injection. After the measurement at 5 h, when the increase in temperature had reached a plateau, the LPS-injected rats were given either the vehicle (1% methocel) or a test compound orally to determine whether the compound could reverse the pyrexia. Percent reversal of the pyrexia was calculated using the rectal temperature obtained at 7 h in the control (vehicle-treated) group as the reference (zero reversal) point. Complete reversal of pyrexia to the pre-LPS baseline value is taken as 100%.

LPS-Induced Pyrexia in Conscious Squirrel Monkeys

Temperature probes were surgically implanted under the abdominal skin in a group of squirrel monkeys (*Saimiri sciureus*) (1.0 - 1.7 kg). This allows for the monitoring of body temperature in conscious, unrestrained monkeys by a telemetric sensing system (Data Sciences International, Minnesota). The animals were fasted and were placed in individual cages for acclimatization 13 - 14 h before use. Electronic receivers were installed on the side of the cages which pick up signals from the implanted temperature probes. At approximately 9:00 a.m. on the day of the experiment, the monkeys were restrained temporarily in training chairs and were given a bolus I.V. injection of LPS, (6 µg/kg, dissolved in sterile saline). The animals were returned to their cages and body temperature was recorded continuously every 5 min. Two h after injection of LPS, when the body temperature had increased by 1.5 - 2°C, the monkeys were dosed orally with either vehicle (1% methocel) or a test compound (3 mg/kg). One hundred minutes later, the difference between the body temperature and the baseline value was determined. Percent inhibition was calculated taking the value in the control group as 0% inhibition.

Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

Experiments were performed using male Sprague Dawley rats (90-110g). Hyperalgesia to mechanical compression of the hind paw was induced by intraplantar injection of carrageenan (4.5 mg into one hind paw) 3 h previously. Control animals received an equivalent volume of saline (0.15 ml intraplantar). A test compound (0.3-30 mg/kg, suspended in 0.5% methocel in distilled water) or vehicle (0.5% methocel) was administered orally (2ml/kg) 2 h after carrageenan. The vocalisation response to compression of the hind paw was measured 1 h later using a Ugo Basile algesiometer.

Statistical analysis for carrageenan-induced hyperalgesia was performed using one-way ANOVA (BMDP Statistical Software Inc.). Hyperalgesia was determined by subtracting the vocalisation threshold in saline injected rats from that obtained in animals injected with carrageenan. Hyperalgesia scores for drug-treated rats were expressed as a percentage of this response. ID_{50} values (the dose producing 50% of the maximum observed response) were then calculated by nonlinear least squares regression analysis of mean data using GraFit (Erithacus Software).

Adjuvant-Induced Arthritis in Rats

Seventy, 6.5-7.5 week old, female Lewis rats (body weight ~146-170 g) were weighed, ear marked, and assigned to groups (a negative control group in which arthritis was not induced, a vehicle control group, a positive control group administered indomethacin at a total daily dose of 1 mg/kg and four groups administered with a test compound at total daily doses of 0.10-3.0 mg/kg) such that the body weights were equivalent within each group. Six groups of 10 rats each were injected into a hind paw with 0.5 mg of *Mycobacterium butyricum* in 0.1 ml of light mineral oil (adjuvant), and a negative control group of 10 rats was not injected with adjuvant. Body weights, contralateral paw volumes (determined by mercury displacement plethysmography) and lateral radiographs (obtained under Ketamine and Xylazine anesthesia) were determined before (day -1) and 21 days following adjuvant injection, and primary paw volumes were determined before (day -1) and on days 4 and 21 following adjuvant injection. The rats were anesthetized with an intramuscular injection of 0.03 - 0.1 ml of a combination of Ketamine (87

mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant. The radiographs were made of both hind paws on day 0 and day 21 using the Faxitron (45 kVp, 30 seconds) and Kodak X-OMAT TL film, and were developed in an automatic processor. Radiographs were evaluated for changes in the soft and hard tissues by an investigator who was blinded to experimental treatment. The following radiographic changes were graded numerically according to severity: increased soft issue volume (0-4), narrowing or widening of joint spaces (0-5) subchondral erosion (0-3), periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative joint changes (0-3). Specific criteria were used to establish the numerical grade of severity for each radiographic change. The maximum possible score per foot was 26. A test compound at total daily doses of 0.1, 0.3, 1, and 3 mg/kg/day, Indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) were administered per os b.i.d. beginning post injection of adjuvant and continuing for 21 days. The compounds were prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

Two-factor ('treatment' and 'time') analysis of variance with repeated measures on 'time' were applied to the % changes for body weight and foot volumes and to the rank-transformed radiographic total scores. A *post hoc* Dunnett's test was conducted to compare the effect of treatments to vehicle. A one-way analysis of variance was applied to the thymic and spleen weights followed by the Dunnett's test to compare the effect of treatments to vehicle. Dose-response curves for % inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a nonlinear least squares' regression. ID_{50} was defined as the dose corresponding to a 50% reduction from the vehicle and was derived by interpolation from the fitted 4-parameter equation.

PHARMACOKINETICS IN RATS

Per Os Pharmacokinetics in Rats

PROCEDURE:

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

Male Sprague Dawley rats (325-375 g) are fasted overnight prior to each PO blood level study.

The rats are placed in the restrainer one at a time and the box firmly secured. The zero blood sample is obtained by nicking a small (1 mm or less) piece off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top to the bottom to milk out the blood. Approximately 1 mL of blood is collected into a heparinized vacutainer tube.

Compounds are prepared as required, in a standard dosing volume of 10mL/kg, and administered orally by passing a 16 gauge, 3" gavaging needle into the stomach.

Subsequent bleeds are taken in the same manner as the zero bleed except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and milked/stroked as described above into the appropriately labelled tubes.

Immediately after sampling, blood is centrifuged, separated, put into clearly marked vials and stored in a freezer until analysed.

Typical time points for determination of rat blood levels after PO dosing are:

0, 15min, 30min, 1h, 2h, 4h, 6h

After the 4 hr time point bleed, food is provided to the rats *ad libitum*. Water is provided at all times during the study.

Vehicles:

The following vehicles may be used in PO rat blood level determinations:

PEG 200/300/400: restricted to 2 mL/kg
Methocel 0.5% - 1.0%: 10mL/kg
Tween 80: 10mL/kg

Compounds for PO blood levels can be in suspension form. For better dissolution, the solution can be placed in a sonicator for approximately 5 minutes.

For analysis, aliquots are diluted with an equal volume of acetonitrile and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with UV detection. Quantitation is done relative to a clean blood sample spiked with a known quantity of drug. Bioavailability (F) is assessed by comparing area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUCpo}{AUCiv} \times \frac{DOSEiv}{DOSEpo} \times 100\%$$

Clearance rates are calculated from the following relation:

$$CL = \frac{DOSEiv(mg/kg)}{AUCiv}$$

The units of CL are mL/h•kg (milliliters per hour kilogram)

Intravenous Pharmacokinetics in Rats

PROCEDURE:

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

Male Sprague Dawley (325-375 g) rats are placed in plastic shoe box cages with a suspended floor, cage top, water bottle and food.

The compound is prepared as required, in a standard dosing volume of 1 mL/kg.

Rats are bled for the zero blood sample and dosed under CO_2 sedation. The rats, one at a time, are placed in a primed CO_2 chamber and taken out as soon as they have lost their righting reflex. The rat is then placed on a restraining board, a nose cone with CO_2 delivery is placed over the muzzle and the rat restrained to the board with elastics. With the use of forceps and scissors, the jugular vein is exposed and the zero sample taken, followed by a measured dose of compound which is injected into the jugular vein. Light digital pressure is applied to the injection site, and the nose cone is removed. The time is noted. This constitutes the zero time point.

The 5 min bleed is taken by nicking a piece (1-2 mm) off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top of the tail to the bottom to milk the blood out of the tail. Approximately 1 mL of blood is collected into a heparinized collection vial. Subsequent bleeds are taken in the same fashion, except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and bled, as described above, into the appropriate labelled tubes.

Typical time points for determination of rat blood levels after I.V. dosing are either:

0, 5 min, 15min, 30min, 1h, 2h, 6h

or 0, 5 min, 30min, 1h, 2h, 4h, 6h.

Vehicles:

The following vehicles may be used in IV rat blood level determinations:

Dextrose:	1mL/kg
2-Hydroxypropyl-β-cyclodextrin	1mL/kg
DMSO (dimethylsulfoxide):	Restricted to a dose volume of 0.1 mL per animal
PEG 200:	Not more than 60% mixed with 40% sterile water - 1mL/kg

With Dextrose, either sodium bicarbonate or sodium carbonate can be added if the solution is cloudy.

For analysis, aliquots are diluted with an equal volume of acetonitrile and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with UV detection. Quantitation is done relative to a clean blood sample spiked with a known quantity of drug. Bioavailability (F) is assessed by comparing area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUCpo}{AUCiv} \times \frac{DOSEiv}{DOSEpo} \times 100\%$$

Clearance rates are calculated from the following relation:

$$CL = \frac{DOSEiv(mg/kg)}{AUCiv}$$

The units of CL are mL/h•kg (milliliters per hour kilogram)

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C,

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C.,

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and `d' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

(vi) yields are given for illustration only;

(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLES

Examples 1, 5, 7, 9, 11, 13 and 17 were prepared according to the sequence of reactions described for Example 3 by replacing benzoyl chloride in Step 1 with the appropriate aroyl chloride and/or 4-methyl-4-hydroxyvaleric acid γ-lactone in Step 2 with the appropriate γ-butyrolactone.

Examples 2, 6, 8, 10, 12 and 14 were obtained by chromatographic separation at the Step 4 in the preparation of Examples 1, 5, 7, 9, 11 and 13 respectively.

4-methyl-4-hydroxyvaleric acid γ-lactone, , Tscheschlok, K., Bäuml, K., Pock, R., Mayr, H. *Tet. Lett.*, 29, 6925, 1988.

3,3-Dimethyl-γ-butyrolactone, Bailey, D.M., Johnson, R.E., *J. Org. Chem.*, 35, 3574, 1970.

EXAMPLE 1

3-[(E)-1-(4-(Methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone

m.p. 146-147°C, Analysis calculated for $C_{18}H_{16}O_4S$
C, 65.84; H, 4.91, S, 9.76 Found: C, 65.73; H, 5.00; S, 10.00

EXAMPLE 2

3-[(Z)-1-(4-(Methylsulfonyl)phenyl)-1-phenyl]methylidene]tetrahydro-2-furanone

m.p. 211-212°C, Analysis calculated for $C_{18}H_{16}O_4S$.
C, 65.84; H, 4.91; S, 9.76 Found: C, 65.75; H, 5.01; S, 9.97

EXAMPLE 3

5,5-Dimethyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone

Step 1: (4-(Methylthio)phenyl) phenyl ketone

A 3 L RBF equipped with a mechanical stirrer was charged with $AlCl_3$ (152 g) and $CHCl_3$ (1.4 L) and cooled in an ice bath. Then benzoyl chloride (139 mL) was added over 0.5 h to the ice-cold suspension. Keeping the internal temp. <10°C, thioanisole was added dropwise over 1 hr. After completion of addition, the resulting mixture was stirred at r.t. for 2 h. The resulting dark red-orange suspension was poured onto an ice-water mixture and stirred until decoloration. The organic layer was separated, washed with water, saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to dryness. The resulting white solid was swished in hexane (500 mL) collected by filtration to give the title compound as a white solid.
^1H NMR (CD_3COCD_3): δ 2.59 (3H, s), 7.41 (2H, d), 7.55 (2H, t), 7.64 (1H, m), 7.75 (4H, m).

Step 2: 3-[Hydroxy(4-(methylthio)phenyl)phenylmethyl]-5,5-dimethyltetrahydro-2-furanone, mixture of erythro and threo isomers

To a solution of 1.0 M LDA (3.9 mL) cooled to -78°C, was added dropwise a solution of 4-methyl-4-hydroxyvaleric acid γ-lactone (440 mg) in THF (4 mL) over 5 min. and the reaction was allowed to proceed at this temp. for 0.5 h. Then a solution of (4-(methylthio)phenyl) phenyl ketone (905 mg) from Step 1, in THF (4 mL) was added dropwise and the resulting mixture was stirred at -78°C for 2 h. The reaction was treated with a 25% aqueous solution of NH_4OAc (50 mL) and extracted with EtOAc (2x50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was partly purified by filtration on a plug of silica gel eluted with 20% EtOAc in hexane to give the title compound as a light yellow solid mixture of diastereomers.
^{1}H NMR (CD_3COCD_3): δ 1.34 and 1.42 (6H, 2s), 1.95 (1H, m), 2.11 (1H, m), 2.45 (3H, s), 4.45 (1H, dd), 4.67 (1H, s), 7.18 (3H, m), 7.27 (2H, q), 7.44 (1H, d), 7.51 (1H, d), 7.56 (1H, d), 7.61 (1H, d).

Step 3: 5,5-Dimethyl-[3(1-(4-(methylthio)phenyl)-1-phenylmethylidene] tetrahydro-2-furanone, mixture of E and Z isomers.

To a solution of the tertiary alcohol obtained from Step 2 (929 mg) in dichloroethane (25 mL), was added Et_3N (1.7 mL) followed by methanesulfonyl chloride (0.8 mL). The resulting mixture was stirred at 70°C for 20 h, allowed to cool to r.t., diluted with water (100 mL) and extracted with EtOAc (2x 75 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (10% EtOAc in toluene) to give the title compound.
^{1}H NMR (CD_3COCD_3): δ 1.42 (6H, 2s), 2.52 (3H, 2s), 2.93 and 2.99 (2H, 2s), 7.08 - 7.41 (9H, m).

Step 4: 5,5-Dimethyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone

To an ice-cold solution of the methylthio compound obtained from Step 3 (660 mg) in CH_2CL_2 (18 mL) and MeOH (2 mL) was added

MMPP (1165 mg of 80% pure). The resulting mixture was stirred at r.t. for 20 h. The reaction was diluted with EtOAc (150 mL) and half saturated $NaHCO_3$ (100 mL). The mixture was shaken vigorously, layers separated, the organic layer was dried over $MgSO_4$ and concentrated. The crude product was swished in EtOAc (30 mL) to give the fast eluting Z isomer pure, as a white solid. The mother liquors were concentrated and purified by flash chromatography (slow eluting product in 80% - 90% - 100% Et_2O in hexane) and then swished in a 1:1 mixture of EtOAc/hexane (10 mL) to afford the title compound as a white solid.

^{1}H NMR (CD_3COCD_3): δ 1.44 (6H, s), 3.00 (2H, s), 3.16 (3H, s), 7.21 (2H, m), 7.33 (3H, m), 7.53 (2H, dd), 7.98 (2H, dd).

Geometry of the olefin was assigned by a nOe experiments.

EXAMPLE 4

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethyl-idene]tetrahydro-2-furanone

The title compound was obtained as a white solid from the first swish (30 mL of EtOAc) in Step 4 of Example 3.

^{1}H NMR (CD_3COCD_3): δ 1.45 (6H, s), 3.03 (2H, s), 3.13 (3H, s), 7.28 (2H, dd), 7.42 (5H, m), 7.90 (2H, d).

Geometry of the olefin was assigned by nOe experiments.

EXAMPLE 5

3-[(E)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl]methyl-idene]tetrahydro-2-furanone

m.p. 186-187°C, Analysis calculated for $C_{18}H_{15}FO_4S$

C 62.42; H, 4.37; S, 9.26 Found: C, 62.72; H, 4.38; S, 9.56

EXAMPLE 6

3-[(Z)-1-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]methyl-idene]tetrahydro-2-furanone.

m.p. 150°C, Analysis calculated for $C_{18}H_{15}FO_4S$
C, 62.42; H, 4.37; S, 9.26 Found: C, 62.83, H, 4.40; S, 9.57.

EXAMPLE 7

3-[(Z)-1-(3-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]methylidene]tetrahydro-2-furanone

m.p. 150-151°C, Analysis calculated for $C_{18}H_{15}FO_4S$
C, 62.42; H, 4.37; S, 9.26 Found: C, 62.60; H, 4.50; S, 9.69

EXAMPLE 8

3-[(E)-1-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]methylidene]-tetrahydro-2-furanone

m.p. 197°C, Analysis calculated for $C_{18}H_{15}FO_4S$
C, 62.42; H, 4.37; S, 9.26 Found: C, 62.57; H, 4.59; S, 9.81

EXAMPLE 9

5-Methyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenyl-methylidene]tetrahydro-2-furanone, Racemic at C-5.

m.p. 132-133°C, Analysis for $C_{19}H_{18}O_4S$
C, 66.65; H, 5.30; S, 9.36 Found C, 66.68; H, 5.35; S, 9.54.

EXAMPLE 10

5-Methyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]-tetrahydro-2-furanone, racemic at C-5.

m.p. 219°C, Analysis calculated for $C_{19}H_{18}O_4S$
C, 66.65; H, 5.30; S, 9.36 Found C, 66.53; H, 5.12; S, 9.19

EXAMPLE 11

3-[(E)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)methylidene]-5,5-dimethyltetrahydro-2-furanone

m.p. 173°C, Analysis calculated for $C_{20}H_{19}FO_4S$
C, 64.16; H, 5.11; S, 8.56 Found: C, 64.00; H, 5.17; S, 8.56

EXAMPLE 12

3-[(Z)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)methylidene]-5,5-dimethyltetrahydro-2-furanone

m.p. 244°C, Analysis calculated for $C_{20}H_{19}FO_4S$
C, 64.16; H, 5.11; S, 8.56 Found: C, 64.00; H, 5.14; S, 8.71

EXAMPLE 13

3-[(Z)-1-(3-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)methylidene]-5,5-dimethyltetrahydro-2-furanone

m.p. 168°C, Analysis calculated for $C_{20}H_{19}FO_4S$
C, 64.16; H, 5.11; S, 8.56 Found: C, 64.04; H, 5.25; S, 8.61.

EXAMPLE 14

3-[(E)-1-(3-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)methylidene]-5,5-dimethyltetrahydro-2-furanone

m.p. 230-231°C, Analysis calculated for $C_{20}H_{19}FO_4S$
C, 64.16; H, 5.11; S, 8.56 Found: C, 63.90; H, 5.14; S, 8.55

EXAMPLE 15

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(2-pyridyl)-methylidene] tetrahydro-2-furanone

Step 1: [4-(Methylthio)phenyl](2-pyridyl)methanol

A solution of 4-bromothioanisole (4.8 g) in THF (140 mL) was cooled to -78°C followed by a slow addition, over 5 min. of 2.5 M n-butyl lithium in hexane (10.2 mL). The resulting suspension was stirred at this temp. for 0.5 h. Then a solution of 2-pyridinecarboxaldehyde (2.32 g) in THF (20 mL) was added over 5 min. the resulting mixture was stirred at -78°C for 0.25 h and at r.t. for 1 h. The reaction mixture was extracted with EtOAc and 25% aqueous solution of NH_4OAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (50% - 60% - 70% EtOAc in hexane) to give the title compound.

^1H NMR (CD_3COCD_3): δ 2.44 (3H, s), 5.26 (1H, d), 5.78 (1H, d), 7.22 (3H, m), 7.38 (2H, d), 7.48 (1H, d), 7.73 (1H, t), 8.51 (1H, d)

Step 2: [4-(Methylthio)phenyl] (2-pyridyl) ketone

To a solution of the compound obtained from Step 1 (3.34 g) in EtOAc (100 mL) was added manganese (IV) oxide in 2 portions (2.50 + 2.72 g) every 24 hours. The resulting suspension was stirred at r.t. for a total of 2 days. The reaction was filtered through a pad of celite, washed with EtOAc and concentrated. The crude product was purified by crystallization from 5% EtOAc in hexane (100 mL) to give the title compound.

^1H NMR (CD_3COCD_3): δ 2.58 (3H, s), 7.38 (2H, d), 7.62 (1H, dd), 7.98 - 8.05 (2H, m), 8.08 (2H, d), 8.72 (1H, d).

Step 3: 3-[Hydroxy(4-(methylthio)phenyl)-2-pyridylmethyl]-5,5-dimethyltetrahydro-2-furanone

Using the procedure described for Example 3, Step 2, and substituting [4-(methylthio)phenyl] (2-pyridyl) ketone obtained from Step 2, for [4-(methylthio)phenyl] (phenyl) ketone, the title compound was obtained as a mixture of erythro and threo isomers after flash chromatography (35% - 50% - 60% EtOAc in hexane).

Fast eluting diastereoisomer ^1H NMR (CD_3COCD_3): δ 1.38 (3H, s), 1.44 (3H, s), 1.82 (1H, dd)m, 2.20 (1H, td), 4.09 (1H, m), 5.82 (1H, 6s), 7.18 (2H, d), 7.28 (1H, dd), 7.50 (2H, d), 7.56 (1H, d), 7.79 (1H, td), 8.50 (1H, d).

Slow eluting diastereoisomer ^1H NMR (CD_3COCD_3): δ 1.40 (6H, s), 2.10 (2H, m), 2.44 (3H, s), 4.60 (1H, t), 6.75 (1H, bs), 7.20 (2H, d), 7.22 (1H, m), 7.63 (2H, d), 7.77 (2H, m), 8.46 (1H, d).

Step 4: 5,5-Dimethyl-3-[(Z)-1-[4-(methylthio)phenyl]-1-(2-pyridyl)methylidene]tetrahydro-2-furanone

To a solution of the tertiary alcohols obtained from Step 3 (351 mg) in CH_2Cl_2 (10 mL) was added dropwise trifluoromethane sulfonic acid (0.6 mL). The reaction was allowed to proceed at r.t. for 0.5 h. The reaction mixture was diluted with Et_3N (2 mL) and the mixture was concentrated in vacuo. The crude product was purified by flash chromatography (50% - 70% EtOAc in hexane) to give the title compound as a gum that solidified upon standing at r.t.

^1H NMR (CD_3COCD_3): δ 1.42 (6H, s), 2.50 (3H, s), 3.07 (2H, s), 7.19 (2H, d), 7.23-7.32 (4H, m), 7.71 (1H, t), 8.53 (1H, d).

Step 5: 5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(2-pyridyl)methylidene]tetrahydro-2-furanone

To a solution of the furanone obtained from Step 4 (436 mg) in MeOH (30 mL) was added a solution of OXONE™ (1.18 g) in water (15 mL). The resulting suspension was stirred at r.t. for 1 h. The reaction was diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (90% - 100% EtOAc in hexane) to give the title compound as a colorless gum. It was further purified by crystallization from a 1:1 mixture of EtOAc and hexane (14 mL) to give a white solid.

m.p. 177°C, Analysis calculated for $C_{19}H_{19}NO_4S$

C, 63.85; H, 5.36; N, 3.92; S, 8.97 Found: C, 63.55; H, 5.33; N, 3.87; S, 9.36

EXAMPLE 16

3-[(Z)-1-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]methylidene]-5,5-dimethyltetrahydro-2-furanone

m.p. 126-127°C, MS (APCI, 3:1 MeOH/aqueous NH_4OAc) m/z calculated for M^+, 390 Found for M^+ +1, 391.

EXAMPLE 17

4,4-Dimethyl-3-[1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone, 1:1 mixture of E and Z isomers.

MS (APCI, 3:1 MeOH/Aqueous NH_4OAc) m/z calculated for M^+, 356 found for M^+ +1, 357.

EXAMPLE 18

4-[Cyclopentyliden(phenyl)methyl]phenyl methyl sulfone

Step 1: Cyclopentyl [4-(methylsulfonyl)phenyl] ketone

Using the procedure described for Example 3, Step 1, and substituting cyclopentanecarbonyl chloride for benzoyl chloride, the title compound was obtained as a beige solid.

^1H NMR (CD_3COCD_3): δ 1.65 (4H, m), 1.75 - 1.95 (4H, m), 2.53 (3H, s), 3.88 (1H, m), 7.34 (2H, d), 7.92 (2H, d).

Step 2: Cyclopentyl[4-(methylsulfonyl)phenyl]phenylmethanol

A solution of the ketone obtained from Step 1 (3.52 g) in Et_2O (50 mL) was cooled to -78°C and was slowly added a 1.8 M solution of phenyl lithium in cyclohexane Et_2O (7:3) (10.0 mL). The reaction was allowed to proceed for 0.25 h. The reaction was diluted with 25% aqueous solution of NH_4OAc and extracted with EtOAc. The organic layer was washed once with water, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (7% EtOAc in hexane) to give the title compound as a yellow oil.

^1H NMR (CD_3COCD_3): δ 1.47 - 1.62 (8H, bm), 2.42 (3H, s), 3.25 (1H, bm), 4.21 (1H, s), 7.08 - 7.16 (3H, m), 7.26 (2H, dd), 7.50 (2H, d), 7.56 (2H, d).

Step 3: 4-[Cyclopentyliden(phenyl)methyl]phenyl methyl sulfide

To a solution of the tertiary alcohol obtained from Step 2 (4.52 g) in CH_2Cl_2 (50 mL) was added dropwise trifluoromethane sulfonic acid (0.1 mL) and the reaction was allowed to proceed for 0.5 h. Et_3N (0.5 mL) was added and the solvents were removed in vacuo. The resulting crude product was purified by flash chromatography (5% EtOAc in hexane) to give the title compound as a colorless gum.

^1H NMR (CD_3COCD_3): δ 1.17 (4H, m), 2.38 (4H, m), 2.49 (3H, s), 7.12 (2H, d), 7.19 (5H, q), 7.32 (2H, t).

Step 4: 4-[Cyclopentyliden(phenyl)methyl]phenyl methyl sulfone

Using the procedure described for Example 3, Step 4, and substituting 4-[cyclopentyliden(phenyl)methyl]phenyl methyl sulfide obtained from Step 3, for 5,5-dimethyl-3[1-(4-(methylthio)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone, the title compound was obtained as a colorless gum.

^1H NMR (CD_3COCD_3): δ 1.66 - 1.73 (4H, m), 2.37 - 2.45 (4H, m), 3.10 (3H, s), 7.20 (2H, d), 7.25 (1H, d), 7.34 (2H, t), 7.46 (2H, d), 7.88 (2H, d).

EXAMPLE 19

2[(E)-1-(4-(Methylsulfonyl)phenyl)-1-phenylmethylidene]-1-cyclopentanone

Chromium trioxide (4.04 g) was suspended in CH_2Cl_2 (35 mL) at -20°C and 3,5-dimethylpyrazole was added in one portion. After stirring for 0.25 h at -20°C, a solution of the compound described in Example 18 (615 mg) in CH_2Cl_2 (4 mL) was added and the reaction mixture was stirred for 1 h while maintaining the temperature at -20°C. Sodium hydroxide (15 mL, 5N) was added and the mixture was stirred for 1 h at 0°C. The reaction was diluted with water and extracted with CH_2Cl_2. The organic layer was washed once with 1N HCl, once with water, once with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (30% - 40% - 50% - 60% EtOAc in hexane) to give 5 compounds one of which was a mixture of the title compound and the compound described in Example 20, Rf 0.10 - 0.08 (30% EtOAc in hexane). These two compounds were separated by preparative HPLC using a Waters μ-porasil column and 40% EtOAc in hexane as eluant. The fast eluting isomer was the title compound. The double bond geometry was assigned by nOe experiments.
High: Res MS, m/z calculated for $C_{19}H_{18}O_3S$+H^+327.10549 Found 327.10558

EXAMPLE 20

2-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]-1-cyclopentanone

The title compound was obtained as the slow eluting isomer during the preparative HPLC separation of Example 19. The double bond geometry was assigned by nOe experiments High, Res. MS, m/z calculated for $C_{19}H_{18}O_3S$+H^+
327.10549 Found 327.10558

EXAMPLE 21

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(3-pyridyl)methylidene] tetrahydro-2-furanone

Using the procedures described for the preparation of Example 15 and substituting 3-pyridinecarboxaldehyde for 2-pyridinecarboxaldehyde in Step 1, the title compound was obtained as a white solid.

m.p. 163 - 164°C, Analysis calculated for $C_{19}H_{19}NO_4S$

C, 68.85; H, 5.36; N, 3.92 Found: C, 63.71; H, 5.24; N, 3.87.

EXAMPLE 22

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(4-pyridylmethylidene] tetrahydro-2-furanone

Using the procedure described for the preparation of Example 15 and substituting 4-pyridinecarboxaldehyde for 2-pyridinecarboxaldehyde in Step 1, the title compound was obtained as a white solid.

m.p. 151°C

EXAMPLE 23

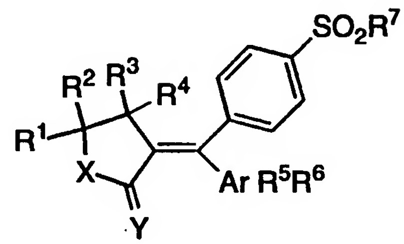
4-[Cyclobutyliden(phenyl)methyl]phenyl methyl sulfone

Using the procedure described for the preparation of Example 18 and substituting cyclobutanecarbonyl chloride for cyclopentanecarbonyl chloride in Step 1, the title compound was obtained as a white solid.

m.p. 121°C

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmacetically acceptable salt thereof wherein
X is selected from the group consisting of

(a) O,
(b) CH_2,
(c) $CH(C_{1-3}alkyl)$,
(d) $C(C_{1-3}alkyl)_2$, and
(e) a bond;

Y is selected from the group consisting of

(a) O,
(b) H,
(c) OH,H;

Ar is selected from the group consisting of

(a) phenyl, and
(b) pyridyl;

each of R^1, R^2, R^3, or R^4 is independently selected from

(a) hydrogen or,
(b) $C_{1-6}alkyl$;

each of R^5 or R^6 is independently selected from

(a) hydrogen,
(b) halo,
(c) $C_{1-4}alkyl$,
(d) $C_{1-4}alkoxy$, and
(e) $C_{1-4}alkylthio$;

R^7 is

(a) NH_2 or

(b) CH_3.

2. A compound according to Claim 1 wherein X is O.

3. A compound according to Claim 1 wherein Y is O.

4. A compound according to Claim 1 wherein X and Y are both O.

5. A compound according to Claim 1 wherein R^1 and R^2 are both CH_3.

6. A compound according to Claim 1 wherein R^5 is hydrogen or F.

7. A compound according to Claim 1 wherein R^7 is CH_3.

8. A compound according to Claim 1 selected from the group consisting of

3-[(E)-1-(4-(Methylsulfonyl)phenyl)-1-phenylmethylidene]-tetrahydro-2-furanone,

5,5-Dimethyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenylmethylidene]tetrahydro-2-furanone,

3-[(E)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl]-methylidene]tetrahydro-2-furanone,

3-[(Z)-1-(3-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylidene]tetrahydro-2-furanone,

5-Methyl-3-[(E)-1-(4-(methylsulfonyl)phenyl)-1-phenyl-methylidene]tetrahydro-2-furanone,

3-[(E)-1-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-methylidene]-5,5-dimethyltetrahydro-2-furanone,

3-[(Z)-1-(3-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-methylidene]-5,5-dimethyltetrahydro-2-furanone,

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(2-pyridyl)methylidene] tetrahydro-2-furanone,

3-[(Z)-1-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylidene]-5,5-dimethyltetrahydro-2-furanone,

4,4-Dimethyl-3-[1-(4-(methylsulfonyl)phenyl)-1-phenyl-methylidene]tetrahydro-2-furanone,

4-[Cyclopentyliden(phenyl)methyl]phenyl methyl sulfone,

2[(E)-1-(4-(Methylsulfonyl)phenyl)-1-phenylmethylidene]-1-cyclopentanone,

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(3-pyridyl)methylidene] tetrahydro-2-furanone,

5,5-Dimethyl-3-[(Z)-1-(4-(methylsulfonyl)phenyl)-1-(4-pyridylmethylidene] tetrahydro-2-furanone, and

4-[Cyclobutyliden(phenyl)methyl]phenyl methyl sulfone.

9. A pharmaceutical composition for treating an inflammatory disease susceptable to treatment with an non-steroidal anti-inflammatory agent comprising:
a non-toxic therapeutically effective amount of a compound according to any one of Claims 1 to 8 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:
a non-toxic therapeutically effective amount of a compound according to any one of Claims 1 to 8 and a pharmaceutically acceptable carrier.

11. A method of treating an inflammatory disease susceptable to treatment with an non-steroidal anti-inflammatory agent comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

12. A method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.

13. A non-steroidal anti-inflammatory pharmaceutical composition comprising an acceptble anti-inflammatory amount of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

14. A selective COX-2 inhibitor pharmaceutical composition comprising an acceptable, selective COX-2 inhibiting amount of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

15. Use of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

16. Use of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cyclooxygenase mediated diseases advantageously treated by an agent that selectively inhibits COX-2 in preference to COX-1.

17. Use of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, as a non-steroidal anti-inflammatory agent.

18. Use of a compound of formula (I), as defined in Claim 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, as a selective COX-2 inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 98/00302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/58 A61K31/34 C07D405/06 C07C317/24 C07C317/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GILBERT ET AL.: "Inhibition of Prostaglandin Sinthetase by Di- and Triphenylethylene Derivatives: A Structure-Activity Study" J.MED.CHEM., vol. 26, no. 5, 1983, pages 693-699, XP002069801 see page 695; table IV	1-21
Y	FRIESEN R W ET AL: "NOVEL 1,2-DIARYLCYCLOBUTENES: SELECTIVE AND ORALLY ACTIVE COX-2 INHIBITORS" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 22, 19 November 1996, pages 2677-2682, XP000197596 see the whole document	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 1998	12/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

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INTERNATIONAL SEARCH REPORT

Inte...ional Application No
PCT/CA 98/00302

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 05643 A (TEULON JEAN MARIE ;LAUNAY MICHELE (FR); NICOLAI ERIC (FR); POTIN D) 12 February 1998 see the whole document ---	1,5-21
P,X	WO 97 37984 A (TEULON JEAN MARIE ;NICOLAI ERIC (FR); UNION PHARMA SCIENT APPL (FR) 16 October 1997 see the whole document -----	1-21

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 98/00302

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		AU 3944397 A	25-02-1998
		US 5686460 A	11-11-1997
WO 9737984 A	16-10-1997	FR 2747123 A	10-10-1997
		FR 2747124 A	10-10-1997
		AU 2393397 A	29-10-1997